UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/373,403	08/12/1999	WILLIAM R. ARATHOON	P1099C1	2534

9157 7590 11/20/2002

GENENTECH, INC.
1 DNA WAY
SOUTH SAN FRANCISCO, CA 94080

EXAMINER	
HOLLERAN, ANNE L	

ART UNIT	PAPER NUMBER
1642	21

DATE MAILED: 11/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/373,403	ARATHOON ET AL.	
	Examiner	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5?
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The response to the restriction requirement, filed May 16, 2002 is acknowledged. Upon further consideration the restriction requirement is withdrawn.

Claims 30-49 are pending and examined on the merits.

Oath/Declaration

2. Two declarations have been submitted for this application. One in which four inventors are listed (Arathoon, Carter, Merchant and Presta) and in which the first name of inventor Arathoon has been omitted, and one in which only one inventor is listed (Arathoon). It is assumed that the corrective inventive entity is Arathoon, Carter, Merchant and Presta. However, because of the presence of the two declarations, the inventive entity is called into question. Therefore, a new oath or declaration is required that lists all of the inventors, with their correct first full names, is required.

Specification

3. The specification is objected because of the following informalities: text is missing from the top of "Appendix 1-15" due to holes that were punched at the top of the pages to attach the specification to the file wrapper. The top margin appears to be too small to accommodate the hole puncing.

The specification is also objected because of the position of the phrase "What is claimed is:". The Appendix directly follows this phrase, making it appear that the Appendix is being claimed.

It is suggested that applicant cancel by amendment the incomplete "Appendix" and provide a new copy of the information to be presented in tables that are inserted into the text of the specification. Thus, the claims will directly follow the text of "What is claimed is:". References to the appendices in the text of the specification should then be amended to recite "Tables".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. Claims 30-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 30 is indefinite because it is drawn to a method for making multispecific antibodies that comprise at least two peptides, but the method steps appear to be drawn to methods where a host cell is cultured, where the host cell comprises a nucleic acid (one molecule) that encodes the two (or more) polypeptides as one molecule instead of two separate molecules.

Claim 33 is indefinite because of the phrases "altering the original nucleic acid encoding the first polypeptide to encode an import residue...". This wording allows the interpretation that

claim 33 is drawn to method using a nucleic acid that encodes only an import residue, and not a nucleic acid that encodes a polypeptide.

Claim 39 is indefinite because the phrase "the heteromultimer" lacks antecedant basis.

Claim 39 is also indefinite because it is drawn to a method for making an immunoadhesin, but depends from claim 30, which is drawn to a method for making a multispecific antibody.

Claim 41, and dependent claim 42, are indefinite because they depend from a canceled claim.

Claim 43 is indefinite because of the following phrase: "comprising an amino acid residue in the interface of the first polypeptide is replaced with...".

Claim 43 is also indefinite because "the bispecific antibody" lacks antecedant basis.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 30-32, 37, 40, and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Carter (WO 93/06217; published 4/1993; cited in the IDS).

Claims 30-32, 37, and 40 are drawn to methods for making a multispecific antibody comprising at least two polypeptides, wherein the polypeptides comprise multimerization

domains, binding domains, wherein the binding domains comprise heavy and light chains, and wherein the light chains comprise a common sequence. The phrase "a common sequence" is broadly interpreted to encompass light chains that have even only one amino acid sequence in common. The methods comprise culturing a host cell with a nucleic acid encoding two polypeptides and recovering the multispecific antibody. Claim 41 is drawn to a host cell comprising a nucleic acid encoding a heteromultimer.

Carter teaches methods for making bifunctional $F(ab')_2$ antibodies (pages 8-9), comprising domains comprising cysteinyl resitidues as multimerization domains. Carter teaches host cells that are E. coli. Thus, Carter teaches methods and host cells that are the same as that claimed.

6. Claims 30, 31, 37, 40, 41 and 42 are rejected under 35 U.S.C. 102(b) as being anticipated by Tso (WO 93/11162; published 6/1993; cited in the IDS).

Claims 30, 31, 37 and 40 are drawn to methods for making a multispecific antibody comprising at least two polypeptides, wherein the polypeptides comprise multimerization domains, binding domains, wherein the binding domains comprise heavy and light chains, and wherein the light chains comprise a common sequence. The phrase "a common sequence" is broadly interpreted to encompass light chains that have even only one amino acid sequence in common. Claims 41 and 42 are drawn to host cells.

Tso teaches methods for making bispecific antibodies that comprise leucine zipper motifs as multimerization domains. Tso teaches host cells and mammalian host cells (page 16). Thus, Tso teaches methods and host cells that are the same as that claimed.

7. Claims 30-42 are rejected under 35 U.S.C. 102(e) as being anticipated by Carter (U.S. Patent 5,731,168; issued March 24, 1998; filing date March 1995).

Claims 30-40 are drawn to methods for making a multispecific antibody comprising at least two polypeptides, wherein the polypeptides comprise multimerization domains, binding domains, wherein the binding domains comprise heavy and light chains, and wherein the light chains comprise a common sequence. The phrase "a common sequence" is broadly interpreted to encompass light chains that have even only one amino acid sequence in common. Claims 41 and 42 are drawn to host cells.

Carter teaches methods for making multispecific antibodies (and immunoadhesins), where the multispecific antibodies and immunoadhesins comprise multimerization domains formed by amino acid residues that form protuberances in one polypeptide chain and cavities in another polypeptide chain. Carter teaches the import residues that replace arginine, phenylalanine, tyrosine, or tryptophan. Carter teaches import residues that replace glycine, alanine, threonine, or valine, and where the import residue is not a cysteine. Carter teaches methods where the two polypeptides each comprise a C_H3 domain or IgG. Carter teaches host cells (see the claims). Thus, Carter teaches methods and host cells that are the same as that claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 30-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vaughan (Nature Biotechnology, 14: 309-314, 1996; cited in the IDS) in view of Bosslet (U.S. Patent 5,591,828; issued Jan. 7, 1997; effective filing date of 6/20/1990) and further in view of either Ridgway (Protein Engineering, 9: 617-621, 1996; cited in the IDS), Carter (U.S. Patent 5,807,706; issued September 15, 1998; effective filing date of March 1, 1995) or Carter (WO 96/27011; published September 1996; cited in the IDS).

Claims 30-42 may be interpreted to be drawn to methods and host cells where the two or more polypeptide comprise identical light chains because of the phrase common sequence. Claims 43-49 appear to be drawn to methods for making multispecific antibodies, where the light chain is identical.

Vaughan teaches an example of two scFvs where identical light chains are paired with two different heavy chains to bind to two different antigens, DTPA and CEA.

Vaughan fails to teach a bispecific antibody made from the two scFvs.

Bosslet teaches bispecific antibodies where one specificity is to an anti tumor antigen and the other is to a chelating agent such as DTPA (see abstract).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a bispecific antibody where the two binding regions comprised identical light chains because Vaughan teaches that scFvs for DTPA and CEA can be found where the each scFv binds to a separate antigen, but has a light chain in common. One would have been motivated to have make such a bispecific scFv because CEA is a known cancer antigen and DTPA is a known chelating agent often used to chelate radioactive moieties. Thus, the bispecific pairing of anti-CEA with anti-DTPA would be used to target tumors bearing the CEA antigen with radioactive moieties chelated via the DTPA binding portion of the bispecific scFv.

Neither Vaughan nor Bosslet teaches bispecific antibodies that comprise multimerization domains.

However, either Ridgeway, Carter (U.S.) or Carter (WO) teach methods for engineering multimerization domains comprising antibody CH3 regions onto polypeptides comprising heavy

and light chain variable domains of antibodies and teach making bispecific antibodies (see abstract, page 620, col. 2, fourth full paragraph of Ridgway; abstract of Carter (U.S.); page 6-7 of Carter (WO)). The Knobs and Holes multimerization domain of Ridgway , Carter (U.S.) or Carter (WO) forms an interface in which the interaction is between a cavity of one multimerization domain and a protuberance of a second multimerization domain.

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have engineered a bispecific antibody by the method of Ridgway, Carter (U.S.) or Carter (W.O). One would have been motivated to use the methods of Ridgeway, Carter (U.S.) or Carter (WO) because of the benefits of using such domains when making bispecific antibodies.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

ALH

Anne L. Holleran
Patent Examiner
November 18, 2002

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600